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**(71) Applicant : KOREA RESEARCH INSTITUTE OF
CHEMICAL TECHNOLOGY
Daedeog-danji, 100 Chang-don
Chung-ku, Daejun-si (KR)**

**(72) Inventor : Lee, Haibung
103-901 Hyundai Apt., 431 Doryong-dong
Yousung-ku, Daejun-si (KR)
Inventor : Yuk, Soonhong
5-1305 Kolon Apt., Nae-dong
Seo-ku, Daejun-si (KR)**

**(74) Representative : Newstead, Michael John et al
Page Hargrave Temple Gate House Temple
Gate
Bristol BS1 6PL (GB)**

(54) Microencapsulation for controlled oral drug delivery system.

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EP 0 480 729 A1

BACKGROUND OF THE INVENTION

(1) Field of the Invention

5 This invention relates to a microencapsulation for the preparation of controlled oral drug delivery system. In particular, it relates to a microencapsulation method of an oil droplet containing a drug for oral administration.

Especially, it relates to a microencapsulation method of a drug for oral administration using the biodegradable and bio-compatible material such as polysaccharide that have a metal chelating capacity for the purpose of minimizing the gastric upset or the damages on the stomach.

10 More especially, it relates to a microencapsulation method of oil containing drugs for oral administration using the biodegradable and biocompatible material such as polysaccharide for the purposes of minimizing the degradation of drug caused by hepatic first-pass metabolism by inducing lymphatic absorption of drug, and the degradation of drug in the strong acidic condition of gastric juice.

Recently, research groups have focused their studies on the desirable drug carrier system because the existing method for medicating drugs by oral administration or injection, have many problems on:-

- 1) the degradation of drug by hepatic first-pass metabolism;
- 2) the severe gastric upset or damages on the stomach by drug's activity;
- 3) the degradation of drug in the stomach by the strong acidic condition of gastric juice.

15 However, the existing methods for drug administration using oral route or injection, have been used because of their convenience to take medicine.

Although in principle the entire gastrointestinal tract is capable of drug absorption, the small intestine is the major site of absorption for drug.

A drug molecule, after diffusing through the mucosa of the intestine, is accessible to both the lymphatic and blood circulation.

25 If a drug is administered via the oral route, it must pass through gut wall and then through the liver before reaching the systemic circulation and its site of action. Extensive hepatic first-pass metabolism in the liver is often encountered, and a fraction of the dose administered may be eliminated before reaching the systemic circulation.

Accordingly, the increased amount of drug dose and dosing frequency are required to maintain blood levels within the therapeutic range. This results in the severe gastric upset or damages on stomach.

30 More, for a cancer patient, the anticancer drugs given orally cause adverse effects because most anti-tumour agents are not selective, but are highly toxic for both cancer and normal cells.

In lymphatic absorption, drug molecules enter directly into systemic circulation by bypassing the liver. Thus, the overall blood levels of drugs which undergo significant metabolism in the liver can be significantly increased if they can be directed to the lymphatic fluid.

35 In general, the lymphatic system is not an important route for drug entry into the body except for highly lipophilic compound, such as dietary fat, cholesterol, and lipid soluble vitamins.

Here, in order to use the advantages of the lymphatic system as drug absorption route, we attempted to use emulsion as drug carrier systems to transport medical drug.

40 The oil emulsions are absorbed easily into lymphatic capillaries transported to regional lymph node.

As a result, the oil emulsion can be considered as drug carriers to the lymphatic system by oral administration as well as by injection into tissues.

Accordingly, an emulsion containing anticancer agent is available in chemotherapeutic drug dosage form for lymph node metastasis, which is most common in human cancer.

45 But, in the case of oral administration of the emulsion containing anticancer drug the most of anticancer drugs are released in the stomach. So, anticancer agents can not reach in the small intestine. Thus, in the case of oral administration, the chemotherapeutic effect of anticancer drug is limited only on the stomach cancer. (CRC : Critical Review in Therapeutic Drug Carrier Systems, vol. 2 No. 3, pp. 245, 1986)

50 (2) Description of the prior Art

As the conventional method for microencapsulating the liquid fatty material like oil emulsion, U.S. Pat. No. 3,008,083; 3,749,799; and 3,819,838 disclose a solidification method of the capsule material, gelatin, by rapidly lowering the temperature and subsequent dehydration. While methods such as those disclosed in the patent literature set forth above have achieved some significant commercial success, difficulties have been sometimes encountered in rapidly inducing solidification of the microencapsulating material.

British Pat. No. 2,086,835 provides a process for encapsulating oils using polysaccharide as material for bead matrix. However this method produces shape-rataing, substantially water insoluble micro-beads contain-

ing a number of thousand oil droplet in the bead matrix.

This process can not provide a microencapsulated emulsion which is individually microencapsulated oil droplet in the powdery state(diameter: less than 5 μ m).

Japan Pat. So 59-228930 provides a process for encapsulating olive oil using sodium alginate as capsule material. In this method, the core and capsule materials flow down as double layers on the vertical cone vibrated
5 supersonically and the microcapsule are received in hardening solution or dried to harden the capsule material.

This method presented in Japan Pat. So 59-228930 must require the very complexed apparatus for micro-encapsulation.

10 SUMMARY OF THE INVENTION

This invention provides the microencapsulation method of oil droplet containing drugs for oral administration. The microencapsulated emulsion obtained in this invention represses the drug release from the emulsion and protects the emulsion and drug from the strong acidic condition of gastric juice. The oil droplet and
15 drugs dispersed in the oil droplet were released rapidly in the small intestine with the disintegration of capsule material.

That is, this present invention provides the drug carrier system for oral administration which improves the prior method using biodegradable and biocompatible natural polymer such as polysaccharide which has a metal chelating capacity.

20 This present invention specifically provide microencapsulation method of oil droplet containing drug for oral administration. The microencapsulated emulsion obtained in this invention can reduce the gastric upset or damages on the stomach and can minimize the degradation of drug caused by hepatic first-pass metabolism, by inducing lymphatic absorption.

Embodiments of the present invention will now be described as follows.

25 First of all, the drug is mixed with liquid oil by sonication for 5-30 seconds to disperse the drug homogeneously in the oil phase. The drug-dispersed oil phase to be incorporated into the microcapsule is added to the aqueous solution mixture(to be used as capsule material) of polysaccharide which has metal chelating capacity, biocompatible and water soluble polymer(to improve the physical property of capsule material), and emulsifying agents. The two phase system (oil/aqueous solution mixture) is subjected to the soni-
30 cation to produce an oil-in-water emulsion containing the drug-dispersed oil droplets in the 1-5 μ m range of diameter.

As soon as possible after formation of the emulsion, it is added to multivalent cation-containing solution to harden the capsule material.

35 Finally, the microencapsulated emulsion is freeze-dried to obtain a final product in powdery state which is the subject of this invention.

The polysaccharide which has a metal chelating capacity, in this invention, include sodium alginate, pectin, xanthomonas campestris (XCPS), and carboxymethylcellulose (CMC).

40 The alginic acid family of linear 1-4 linked glycuronans are the copolymers composed of ~D-mannopyranuronic acid (M) residue and α -L-gulopyranuronic acid (G) residues that are arranged in homopolymeric (GG and MM) and heteropolymeric (MG) sequences in varying proportions and distribution patterns. Alginic acid can be derived from algal or bacterial sources.

In the invention, sodium salt of alginic acid was used as microcapsule material. Sodium alginate is water-soluble and has a good biodegradability, and sodium alginate is widely used for food, cosmetics, medicine, and pharmaceuticals, because it is biodegradable and biocompatible material without immunogenic effect.

45 The biocompatible polymers used as capsule material mixed with polysaccharide in this invention include polyamino acid, sodium salt of polyacrylic acid, polylactic acid hydroxypropyl methylcellulose, and collagen protein. These polymers are available in markets and are used for cosmetics, toothpaste, shampoo, painting, and adhesives. These polymers are water soluble and mixed with polysaccharide in aqueous solution homogeneously.

50 The desirable mixing ratio of polysaccharide and these polymers is from 100:0 to 20:80.

If the content of these polymer exceeds 80 wt% of solution mixture, the hardened capsule material can not be obtained.

55 The core material in the invention is a liquid oil which is used widely for food or pharmaceuticals. Some representative examples of such liquid oil include corn oil, peanut oil, coconut oil, castor oil, sesame oil, soy bean oil, perilla oil, sunflower oil, and walnut oil.

Any types of drug which is stable on the subjection of sonication can be incorporated to oil phase in this invention. For example, these drugs include steroid drugs, anticancer drug like 5-fluorouracil and me-CCNN, anti-
biotic, and antiulcer drug like omeprazole. The amount of drugs to be incorporated into oil phase in this invention

is a 1-40 wt% of the liquid oil. If the amount of drug is more than 40 wt%, the excess of drug may be extracted from liquid oil.

In this invention, the emulsifying agents are used in the process in order to prepare for the stable oil-in-water emulsion. These emulsifying agents should be nontoxic and nonimmunogenic substances. Some examples of emulsifying agents in the invention include, Tween 20, Tween 40, Tween 80, Bile salt, sodium cholate, a mixture of 80 wt% ethyleneglycol 1000 monocetyether and 20 wt% ethyleneglycol 400, and polyoxyethylenether. The amount of emulsifying agents used in this invention is 5-10 wt% of the total amount of case and capsule material. If the amount of emulsifying agents is less than 0.5 wt%, the emulsion can not be formed.

The amount of aqueous phase of capsule material is a 100-200 wt% of the total amounts of liquid oil and drugs.

Multivalent cation used in this invention include aluminium (Al^{+3}) ions, calcium (Ca^{+2}) ions, or magnesium (Mg^{+2}) ion.

The concentration of cation is 0.5-5 wt% range.

In this present invention, the inventors use emulsification, chelation, and freeze-drying for the preparation of microencapsulated emulsion containing drugs for oral administration instead of temperature dropping and dehydration (disclosed in U.S. Pat. No. 3,608,083, U.S. Pat. No. 3,749,799, and U.S. Pat. No. 3,810,838).

The invention disclosed in british Pat. No. 2,086,835 provides multiply compartmentalized micro-bead and the invention disclosed in Japan Pat. No. 59-288930 provides the diversified microcapsules in their diameter (20-100 μ m size) using the special apparatus for sonication.

It is the advantage of this invention that the powdery microencapsulated emulsions with regular size can be obtained and no special equipment for microencapsulation is required.

The invention will now be further understood from the following non-limiting examples, wherein all percentages are given by weight.

Examples

Example 1

4 parts of 5-fluorouracil (anticancer drug) as a model drug was mixed with 20 parts of corn oil as a core material by sonication for 10 seconds to disperse the drug homogeneously in the oil phase.

The drug-dispersed oil phase to be incorporated into the microcapsule is added to 20 parts of the aqueous solution of 5% sodium alginate (Junsei chemical Co., Ltd. Japan) containing 2.5 parts of bile salt as an emulsifying agent (Sigma Co., Ltd. U.S.). The two phase system (oil/aqueous solution mixture) was subjected to the sonication to produce oil-in-water emulsion containing the drug-dispersed oil droplet in the 1-5 μ m range of diameter. As soon as possible after formation of the emulsion, it was added to 100 parts of 2.5% aluminum sulfate [$Al_2(SO_4)_3$] aqueous solution to harden the capsule material (sodium alginate).

Finally, the microencapsulated emulsion is freeze-dried to obtain a final product in powdery state which is the subject of this invention.

Example 2

The process of Example 1 was repeated except that 2.5% sodium alginate aqueous solution was employed in place of 5% sodium alginate aqueous solution.

Example 3

The process of Example 1 was repeated except that 1% sodium alginate aqueous solution was employed in place of 5% sodium alginate aqueous solution.

Example 4

The process of Example 1 was repeated except that the aqueous solution mixture of 20 parts of 5% sodium alginate aqueous solution and 5 parts of 5% polyamino acid aqueous solution was employed in place of 5% sodium alginate aqueous solution.

Example 5 to 7

The process of Example 1 was repeated except that the aqueous solution mixtures of 20 parts of 5% sodium

alginate aqueous solution and 5 parts of 5% hydroxypropyl methylcellulose(or polyacrylic acid, or collagen) aqueous solution were employed in place of 5% sodium alginate aqueous solution.

Example 8

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The process of Example 1 was repeated except that sodium salicylate was employed as a model drug in place of 5-fluorouracil.

Example 9

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The process of Example 1 was repeated except that omeprazole which degraded rapidly in the strong acidic condition of gastric juice was employed as a model drug in place of 5-fluorouracil.

In this case, the microencapsulated emulsion was obtained as a bead form (the aggregate of powdery microencapsulated emulsion) and the enteric-coated bead with hydroxypropyl methylcellulose phthalate as a capsule material for enteric coating was used as a drug carrier system for omeprazole.

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Example 10 to 12

The process of Example 1 was repeated except that 5% pectin, CMC, and XCPS aqueous solution was employed in place of 5% sodium alginate aqueous solution.

20

Comparative example 1

The process of Example 1 was repeated except that water was employed in place of 5% sodium alginate aqueous solution.

25

Comparative example 2

The process of comparative Example 1 was repeated except that sodium salicylate was employed as a model drug in place of 5-fluorouracil.

30

In Table 1, the release pattern of drugs (5-fluorouracil and sodium salicylate) from the drug carrier system was presented.

The drug carrier systems using the microencapsulated emulsion or emulsion was prepared according to the process described in Examples 1, 8, 10, 11, 12, and Comparative Examples 1, 2. The drug release experiment was performed in artificial gastric juice (pH=2) using dialysis bag.

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Table 1. Drug release pattern in the strong acidic condition (pH=2) of artificial gastric juice.

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Example No.	Amount of released drug (mg)	
	after 3 hours	after 24 hours
Example 1	2.01	9.50
Example 8	8.10	22.8
Example 10	3.52	12.42
Example 11	4.12	14.10
Example 12	3.77	12.94
Comp. example 1	13.5	50.3
Comp. example 2	30.5	100.1

25

The amount of drug released from the drug carrier system was measured at 3 and 24 hours time points.

The result shows that the amount of drug released from the microencapsulated emulsion during first 3 hours is much less than that from emulsion without capsule material (control) indicating that the drug carrier system in this invention can repress the drug release in the strong acidic condition of gastric juice.

30

In addition, it was confirmed by a microscope that the stability of the microencapsulated emulsions in the strong acidic condition of gastric juice was improved significantly in comparison with that of control.

That is, it was observed that the microencapsulated emulsion prepared according to example 1 stayed intact in artificial gastric juice during 24 hour, while the emulsion prepared according to Comparative Example 1 was disintegrated and aggregated during 30 minutes staying in artificial gastric juice.

35

Figure 1 shows the drug release pattern in the artificial gastric juice as a function of the concentration of capsule material. The release amount drug released from the drug carrier system decreases as the concentration of sodium alginate solution used as capsule material increases. This is other evidence that the drug release is hindered by the capsule wall of the microencapsulated emulsion.

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Table 2. The stability of drug carrier system in the artificial gastric juice and the release pattern of omeprazole in the artificial intestinal fluid.

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	Amount of drug carrier system used in each experiment	100mg
10	Loading amount	20mg
	Amount of Omeprazole after staying in the artificial gastric juice for 2 hours (37°C)	18.5mg
15	Amount of released Omeprazole in the artificial intestinal fluid within 10 minutes (37°C)	19mg

20 * All the experiments were performed according to the procedures presented in U.S.P.

25 In Table 2, the stability of Omeprazole in the drug carrier system and the release pattern of the Omeprazole from the drug carrier system were observed using the microencapsulated emulsion as a drug carrier system. The drug carrier system was prepared according to the process described in Example 9 and the model drug was Omeprazole which was degraded rapidly in the gastric juice. More than 90% of total loading amount of Omeprazole remained stable after the stay in the artificial gastric juice(37°C) for 2 hours.

30 This drug carrier system was disintegrated rapidly in the artificial intestinal fluid and more than 90% of Omeprazole in the drug carrier system was released within 10 minutes.

Thus the microencapsulated emulsion in this invention can be used effectively as the drug carrier system for oral drug which is unstable in the gastric juice.

35 As is apparent from the above results, the present invention provides a controlled oral drug carrier system which minimizes the degradation of drug in the gastrointestinal tract and maximizes the absorption of drug in the small intestine.

Claims

40

1. A process for microencapsulation of oil droplet containing medical drug for oral administration, said process comprising the following steps:

45 first, the drug is mixed with liquid oil by sonication for 5-30 seconds to disperse the drug homogeneously in the oil phase; the drug-dispersed oil phase to be incorporated into the microcapsule is added to the aqueous solution mixture(to be used as capsule material) of polysaccharide which has metal chelating capacity, the biocompatible and water-soluble polymer(to improve the physical property of capsule material) and emulsifying agents; the two phase system (oil/aqueous solution mixture) is subjected to the sonication to produce an oil-in-water emulsion containing the drug-dispersed oil droplets in the 1-5µm range of diameter;

50 as soon as possible after formation of the emulsion it is added to multivalent cation-containing solution to harden the capsule material; and

finally, the microencapsulated emulsion is freeze dried to obtain a final product in powdery state which is the subject of this invention.

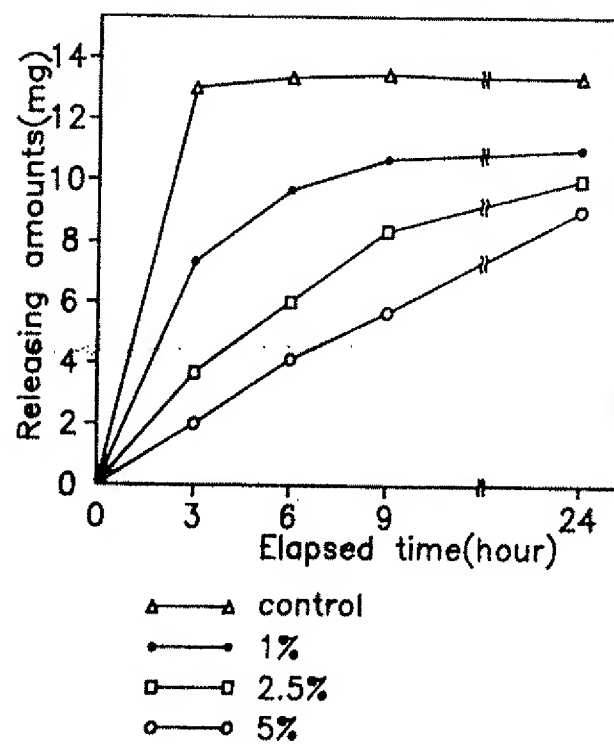
2. The process as claimed in claim 1, wherein the aqueous solution mixture (to be used as capsule material) contains 20-100 weight % of polysaccharide in the aqueous solution mixture.

3. The process as claimed in claim 1, wherein the polysaccharide which has metal-chelating capacity com-

prises pectin, xanthomonas campestris (XCPS), and carboxymethyl cellulose (CMC).

4. The process as claimed in claim 1, wherein the biocompatible and water-soluble polymer comprises hydroxypropyl methylcellulose, water-soluble polyamino acid, the sodium salt of polyacrylic acid and collagen.
5. The process as claimed in claim 1, wherein the oil phase comprises any edible oil such as corn oil, peanut oil, coconut oil, castor oil, sesame oil, soybean oil, perilla oil, sunflower oil and walnut oil.
6. The process as claimed in claim 1, wherein the emulsifying agent comprises any biocompatible emulsifying agent such as Tween 20, Tween 40, Tween 80, sodium cholate, bile salt, a mixture of 80 w/v% polyethylene glycol 1000 mono cetyl ether and 20 w/v% polyethylene glycol 400, and polyoxyethylene ether.
7. The process as claimed in claim 1, wherein the multivalent cation comprises aluminum ion, calcium ion and magnesium ion.
8. The process as claimed in claim 1, wherein the drug comprises any the of drug which is stable on the subsection of sonication such as steroid drug, antibiotic, and antitumour drug, and antiulcer drug which degrades rapidly in strong acidic condition of gastric juice such as Omeprazole.

FIG. 1





European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 91309337.3
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	PATENT ABSTRACTS OF JAPAN, unexamined applications, C section, vol. 2, no. 31, February 27, 1978 THE PATENT OFFICE JAPANESE GOVERNEMENT page 4 221 C 77 * Kokai-no. 52-125 615 (KYOWA MAKKO KOGYO K.K.) *	1,8	A 61 K 9/50 A 61 K 9/51 A 61 K 9/52 A 61 K 9/127 //A 61 K 31/44
Y	US - A - 4 880 634 (P. SPEISER) * Abstract; column 7, lines 1-5; examples 4-15 *	1,2, 4-6,8	
Y	US - A - 4 501 726 (U. SCHRÖDER, K. MOSBACH) * Examples 1,4,7,12 *	1,2, 4-6,8	
A	WO - A - 88/01 506 (T. YING) * Claims 1-3,6; page 10, line 30 - page 11, line 16; page 12, lines 10-16 *	1,2,3, 6,7	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A 61 K 9/00
A	US - A - 4 107 288 (R.C. OPPENHEIM et al.) * Claims 1-3,5; example 1; column 1, line 67 - column 3 line 25 *	1-4,7, 8	
A	EP - A - 0 198 208 (HOECHST AKTIENGESELLSCHAFT) * Abstract; column 10, line 42 - column 12, line 4 *	1,2,5, 8	
A	EP - A - 0 145 240 (TAKEDA CHEMICAL INDUSTRIES, LTD.) * Claims 1,4,9,10; page 8,	1,4	
The present search report has been drawn up for all claims			
Place of search		Date of completion of the search	Examiner
VIENNA		14-01-1992	MAZZUCCO
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document</p>			

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Application Number

-2-

EP 91309337.3

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<p>lines 6-17 *</p> <p>---</p> <p>EP - A - 0 326 026 (BASF AKTIENGESELLSCHAFT) * Claims 1,3,5,9; example 1 *</p>	1,2,5	
A	<p>---</p> <p>EP - A - 0 159 237 (LABORATOIRE L. LAFON SOCIETE ANONYME DITE) * Claims 1,7,8; examples 1,2,5 *</p>	1,2, 4-6	
D,A	<p>---</p> <p>GB - A - 2 086 835 (DAMON CORPORATION) * Claims 1,4,6; examples 1-3,13,14 *</p> <p>----</p>	1,2,7	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
<p>Place of search</p> <p>VIENNA</p>			<p>Date of completion of the search</p> <p>14-01-1992</p>
<p>Examiner</p> <p>MAZZUCCO</p>			
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>***** & : member of the same patent family, corresponding document</p>			

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